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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/144,838	08/31/1998	MICHAEL A. SIANI	GRFN-020/01U	5261

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	38

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.	Applicant(s)
09/144,838	Siani et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 6, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/6/03 has been entered.

2. The present office action contains new objections/rejections as well as modified objections/rejections already of record. Any attorney arguments not already addressed of record, but which are pertinent against the present objections/rejection, will be addressed by the Examiner in the next office action.

Information Disclosure Statement

Applicant requested Examiner consideration of references not previously considered by the Examiner. Applicant is requested to provide a new 1449 listing references and enclose reference and listing of references which were not previously considered by the Examiner.

Status of the Claims

Claims 28-36 are currently pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

4. Applicant's election without traverse of native chemical ligation as the elected species in Paper No. 13 is again acknowledged. Accordingly, a complete reply to the final rejection must include cancellation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment has overcome the new matter rejection of claims 33 and 34 recited in the prior office action.

Applicant's amendment has overcome the rejection of claims 28-31 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Canne et al., JACS Vol. 117 (1995) pages 2998-3007 and Dawson et al. Science Vol. 266 (11/94) pages 776-779 cited in the Canne et al. Reference at page 6588 footnote (13) to demonstrate the inherent teaching of head-to-tail ligation of "the chemical ligation approach to the total chemical syntheses of proteins".

Outstanding Objection(s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

5. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION) .

The claims (28,29,32 and claims dependent thereon), as amended, introduce claim language e.g. "wherein each of said ... **sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin** to permit said peptide segments to mediate the function of said functional domain when incorporated into said cross-over protein "; in which the bolded portion is not supported by the specification disclosure, nor has applicant indicated where such support exists.

6. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (INADEQUATE WRITTEN DESCRIPTION REJECTION).

The specification fails to provide sufficient written description to support a genus of cross-over proteins which are devoid of sequence length, amino acid content, specific biological function which is produced by the presently claimed method of ligating one or more peptide segments derived from one or more first protein(s) and one or more second protein(s) "wherein each of said additional peptide segments exhibit **sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin** to permit said peptide segments to mediate the

function of said functional domain when incorporated into said cross-over protein "; whether of the same or different family or classes.

There is a limited showing of ligating protein fragments from the same "class" of protein (e.g. chemokines: such as RANTES etc.) but no examples regarding the ligation of peptide fragments from different classes. Even within the same "class"; applicant's method would ligate multiple peptide fragments which would lack a common core structure which elicits a common activity; and would additionally broadly encompass both functionally and structurally distinct peptides including hormones, enzymes etc.

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the resulting "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

However, it is clear that applicant has not presented an adequate sample to demonstrate possession of the presently claimed invention. See *University of California v. Eli Lilly and Co.* U.S. Court of Appeals Federal Circuit (CA FC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997 No. 96-1175 regarding adequate disclosure, the analysis of which does not address the absence or presence of undue experimentation.

For the specification discloses only limited examples that are neither representative of the claimed genus (which is not limited by peptide length or amino acid composition nor types of derivations), nor is it clear that they represent a substantial portion of the claimed genus. This showing clearly does not provide an adequate representation regarding the myriad possible cross-over proteins or peptides of different length which lack a common core which would be expected to elicit a common activity.

7. Claims 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canne et al., JACS Vol. 117 (1995) pages 2998-3007, Dawson et al. Science Vol. 266 (11/94) pages 776-779 and Clarke-Lewis et al., J.Biol. Chem. Vol. 269, No. 23 (June 10,1994) pages 16075-16081.

Canne et al. disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one at a time or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries. The Canne reference further teaches the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3). Accordingly, the Canne et al. Reference method discloses the use of reactants (e.g. peptide segments derived from different proteins which comprise different functional domains

e.g. "functional protein module(s)") which are chemoselectively ligated to form "cross over proteins" within the scope of the presently claimed inventions. It is noted that the Canne et al. reference explicitly teaches the ligation of peptide fragments which contain "reactive groups" (e.g. derived carboxyl terminus) that form "cross over proteins".

With respect to the presently claimed invention (as amended) which encompasses head to tail ligation (amino terminal amino acid of a fragment to a carboxyl terminal of a different fragment) to form a cross over protein; it is noted that the Canne et al. reference specifically recites the application of a small number of types of chemical ligation techniques which preferably include the Science article native chemical ligation approach (e.g. see Science article page 777 Fig. 1) which illustrates head-to-tail covalent ligation.

Accordingly, the Canne reference incorporation of the Science reference article describing the native chemical ligation approach (e.g. head to tail ligation) would render its selection from such a limited number of ligation techniques either immediately envisages (e.g anticipated) or alternatively obvious to one of ordinary skill in the art at the time of applicant's invention. E.g. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). As further taught by the Canne reference, "This study demonstrates that a *molecular approach*, wherein *independent functional or structural units are joined by chemical ligations*, is a feasible method of protein syntheses. This technique can construct proteins of unusual structure with full biological activity, thus providing a powerful new way to study important biological phenomena. The **chemical ligation** approach to the total chemical synthesis of proteins has the potential to take protein

syntheses far beyond the realm of nature. Mutually compatible ligation chemistries, such as the thioester- and oxime-forming reactions reported here, can be used for the ligation of a number of different unprotected peptide segments in a convergent manner". See page 3004 up to "Experimental Section".

From the above, citation and the reference article taken as a whole, it is clear that the Canne et al. reference teaches the extension of the Dawson "chemical ligation" approach to incorporate "independent functional or structural units by chemoselective ligation". In this regard, Canne et al. specifically cites the Dawson et al. Reference chemical ligation head-to-tail technique which was introduced by the SAME authors and the general applicability of this technique to all different types of ligation chemistries and peptides (see page 2999, left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided).

Additionally, the Canne et al. Reference teaching taken alone, or in conjunction with the teaching of the Science reference, teaches the making of prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation.

The Canne et al. reference teaching taken alone, or if necessary, further in view of the Dawson reference teaching differs from the presently claimed invention by failing to disclose the selection of peptide segments from chemokine proteins for producing a cross-over protein.

However, Clark-Lewis teach the use of peptide fragments derived from chemokines (e.g. IL-8) comprising two or more functional domains (e.g. CXC and CC chemokine families: see page 16075) for making hybrid proteins comprising peptide fragments comprising IL-8 domain regions [e.g. IL-8, other CXC chemokines and analogs (e.g. homologs thereof) with IP10] in order to determine e.g. structure-activity relationships (SAR's) which include the determination of the structural features critical for IL-8 receptor binding and functional activation; while teaching the desirability of making more analogs/hybrid proteins in order to further elucidate conformational (e.g. 3-D) parameters necessary for chemotactic and exocytic activities. See e.g. abstract; examples and conclusion. .

Accordingly, one of ordinary skill in the art would have been motivated to utilize peptide segments derived from chemokine families (e.g. CXC/CC chemokines such as IL-8 and others) for producing hybrid (e.g. cross-over) proteins in order to determine structure-activity relationships (SAR's) related to functional activity of such chemokine family members.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to select chemokine proteins for producing a cross-over protein using chemoselective ligation as taught by Canne et al. (alone or with Dawson) in order to determine e.g. structure-activity relationships (SAR's) related to such chemokines.

8. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canne et al., Dawson et al. and Clarke-Lewis et al., as applied to claims 28-31 above, and further in view of Pavia eta l., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

To the extent that the Canne et al. reference (alone or in combination with the Dawson reference) and Clarke-Lewis et la. Reference combined teaching described above (herein incorporated by reference in its entirety) differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation; the Pavia et al. Reference is offered.

The Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the Canne reference modular strategy in order to optimize drug discovery.

Thus, modification of the Canne reference method alone or in view of the Science reference ligation technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

Double Patenting

9. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide, with the preferred embodiment being the derivation of such oligopeptides from chemokines (e.g. IL-8: see fig. 7; and examples).

The patent claims fail to teach the use of oligopeptide fragments from different chemokine proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) proteins .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments once or in a multiple manner using

the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

10. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No. 6,184,344 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '344 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase

molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '344 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '344 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

11. Claims 28-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (e.g. claims 1-7) of U.S. Patent No. 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007.

The Patent claims teach native chemical ligation approach (e.g. head to tail ligation) of a first and second oligopeptide.

The patent claims fail to teach the use of oligopeptide fragments from different proteins (e.g. comprising a functional protein module) to form a cross-over (e.g hybrid) protein .

However, the Canne et al. Reference disclose a chemical ligation chemoselective method of making both **hetero-** and homo- **dimers** utilizing a "***modular strategy***" (abstract) (emphasis provided). The Canne et al. method extends the native peptide ligation (e.g. see page 2999, beginning of left paragraph and citation no. 13 to Science article: herein the "Science article") (which is synonymous with the patented claim method) chemoselective technique to other ligation

chemistries (e.g. thioesters, oximes, hydrazones, disulfides, thiazolidones etc.: see page 2999 left column) and to the formation of "complex protein analogues" (not just single protein syntheses as described in the Science article) which would allow for the condensation or more than two (e.g. "Three or more") unprotected **peptide segments** in a specific manner utilizing chemical ligation (emphasis provided). Accordingly, the Canne et al. Reference suggests the use of chemoselective chemical ligation to condense two or more peptide segments one or in a multiple manner using the native chemical ligation strategy (e.g. in the Science article) and/or different chemoselective ligation chemistries.

Accordingly, the Canne reference teaching of the use of chemoselective chemical ligation (e.g. including native chemical ligation) in a modular strategy to generate heterodimers utilizing two or more fragments of transcriptional regulatory proteins (e.g. cMyc and Max) that comprise protein domains (e.g. see schemes and figures especially schemes 1 and 3) would motivate one of ordinary skill in the art to utilize the patented claim process in the Canne modular strategy and thus render obvious the presently claimed invention..

12. Claims 32-36 are rejected under 35 U.S.C. 103(a) as being rejected for obviousness-type double patenting over U.S. Patent No 6,326,468 in view of Canne et al., JACS Vol. 117 (1995) pages 2998-3007 as applied to claims 28-31 above, and further in view of Pavia et al., Biorg. & Medicinal Chem. Lett. Vol. 3, No. 3 pages 387-396.

The '468 and Canne et al. combined teaching of making prospective analogues (e.g. ligands) by chemical ligation of peptide fragments one at a time for biological evaluation differs from the presently claimed invention (e.g. claims 32-36) which is drawn to the making and screening of libraries of ligands for biological evaluation.

However, the Pavia et al. reference teaches that the traditional serial process of synthesizing and testing peptide analogues one at a time is being replaced by the use of combinatorial library syntheses strategies since the libraries provide the ability to increase molecular diversity and utilize high throughput screening which optimizes drug discovery See e.g. Pavia et al. Abstract; page 391 ("Automated Methods").

Accordingly, one of ordinary skill in the art would be motivated to generate libraries of compounds by utilization of the '468 and Canne et al. reference method in order to optimize drug discovery.

Thus, modification of the '468 and Canne et al. reference method technique to utilize combinatorial libraries would have been obvious to one of ordinary skill in the art at the time of applicant's invention in order to optimize drug discovery.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)

April 18, 2003

BENNETT CELSA
PRIMARY EXAMINER